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The Retreat from Precaution: Regulating Diethylstilbestrol (Des), Endocrine Disruptors, and Environmental Health

Author(s): Nancy Langston

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NANCY LANGSTON

# the retreat from precaution: REGULATING

DIETHYLSTILBESTROL (DES), ENDOCRINE DISRUPTORS,  
AND ENVIRONMENTAL HEALTH

## ABSTRACT

Rates of intersexuality, reproductive cancers, and infertility appear to be increasing. Many researchers suspect that a key role is played by endocrine disruptors—the industrial pollutants that mimic hormones and disrupt the endocrine systems that shape sexual development. Yet, for all the concern raised by a flood of experimental research showing endocrine disruption in animals and epidemiological studies suggesting effects on human reproduction, the U.S. government has essentially failed to regulate these chemicals, retreating from a precautionary principle that would require caution in the use of potentially toxic chemicals. Debates in the 1930s and 1940s over the regulation of diethylstilbestrol (DES), the first synthetic estrogen and the first chemical known to act as an endocrine disruptor, show how political pressures, scientific uncertainty, and changing conceptual models of gender and health led to this retreat from precaution.

RATES OF INTERSEXUALITY, reproductive cancers, and infertility appear to be increasing across a broad range of animals, from polar bears to people. Many researchers suspect that a key role is played by endocrine disruptors—industrial pollutants that mimic hormones and alter sexual development, with potentially irreversible effects. In the past decade, hundreds of experimental studies have shown that endocrine disruptors can lead to reproductive problems in laboratory animals and wildlife, while epidemiological studies have found correlations between human exposure to industrial chemicals and reproductive problems in humans. Yet the U.S. government has failed to regulate these chemicals, arguing that because scientists have not proven low-level exposure is the cause of reproductive problems in humans, too much scientific uncertainty remains for regulators to act.

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Environmentalists counter that, even in the absence of certainty, the precautionary principle should apply in the regulation of endocrine disruptors. The precautionary principle states that if an action might cause severe or irreversible harm to complex systems where consequences are unpredictable, the burden of proof should fall on industry to show that potentially toxic chemicals are safe before releasing them into the environment. As Ted Schettler of Greater Boston Physicians for Social Responsibility writes: "The limits of science and rigorous requirements for establishing causal proof often conspire with a perverse requirement for proving harm, rather than safety, to shape public policies which fail to ensure protection of public health and the environment."<sup>1</sup> Industry advocates argue, on the other hand, that application of the precautionary principle would put an end to innovation and potentially life-saving advances.<sup>2</sup>

These are not new debates. The concept of precaution came into widespread American use in the 1990s, yet industries, regulators, and citizens have been arguing over the same principles since the 1930s.<sup>3</sup> This essay examines American debates over precaution and regulation in the 1930s and 1940s, focusing on diethylstilbestrol (DES), the first synthetic estrogen and the first chemical known to act as an endocrine disruptor. Even before the Food and Drug Administration approved the drug in 1941, researchers knew that DES caused cancer and problems with sexual development in laboratory animals. These concerns initially led FDA Commissioner Walter Campbell to reject the drug, arguing that regulators must follow what he called the "conservative principle."<sup>4</sup> FDA regulators essentially adopted the precautionary principle sixty years before that term came into common usage. Yet by 1947, the FDA had abandoned its position of precaution, telling critics of DES that it was up to them to prove that DES had caused harm, rather than up to the drug companies to show that DES was safe.<sup>5</sup> This paper argues that a constellation of political, scientific, and conceptual factors led to this retreat from the precautionary principle in the 1940s. That retreat was at the heart of the DES tragedy and is key to understanding the roots of our current problems with endocrine disruptors.

DES changed the internal ecosystems of human, livestock, and wildlife bodies, interconnecting our bodies with our environments in increasingly troubling ways. Beginning in the 1940s, millions of women were prescribed DES, first as a hormone replacement therapy during menopause, and then to prevent miscarriage during pregnancy. Between 2 million and 5 million pregnant women eventually took the drug in America, exposing themselves, their children, and even their grandchildren to higher rates of reproductive cancers, infertility, and birth defects. DES became an environmental issue as well as a personal health issue. By the 1950s, livestock were implanted with DES to promote rapid weight gain, which enabled the development of an industrialized feedlot system. The metabolic byproducts of DES—wastes with potent estrogenic activity—from feedlots and from people made their way into broader ecosystems, exposing a wide range of wildlife to the hormone, and likely contributing to increases in intersex conditions and reproductive problems.<sup>6</sup>

## DISCOVERING DES

THE SYNTHESIS OF DES occurred as new scientific technologies spurred research into hormones that dramatically changed understandings of sexual differentiation. In the 1920s and 1930s, scientists learned that ovaries produce what at first were defined as “female” hormones, and that production of those hormones declined during menopause. But a simple model—females produce female hormones, which make them female, and males produce male hormones—soon got much more complicated. The historian of medicine Nellie Oudshoorn shows that when endocrinologists realized that both sexes contained both “male” and “female” hormones, “this shift in conceptualization led to a drastic break with the dualistic cultural notion of masculinity and femininity that had existed for centuries.” Oudshoorn argues that this transformed “biological definitions of sex,” for “The model suggested that, chemically speaking, all organisms are both male and female. ... In this model, an anatomical male could possess feminine characteristics controlled by female sex hormones, while an anatomical female could have masculine characteristics regulated by male sex hormones.” A simple “theory of duality (sex difference) was transformed through the bio-chemists’ challenge.”<sup>7</sup> As technologies for envisioning internal characteristics developed, the meaning of sex became less defined by characters visible to the naked eye, and increasingly defined by characters that were hidden from the ordinary gaze.

The belief that sexual difference was fundamental, however, did not vanish, as the gender historian Joanne Meyerowitz shows in *How Sex Changed*. The location of sex difference simply moved from the gonads to the whole body. This shift helped create the concept of the hormonal body, where women, rather than men, were assumed to be far more ruled by their hormones, and therefore in need of medical intervention to transform an unruly wild nature into a regulated order.<sup>8</sup>

Medical researchers constructed a model that they believed explained the decline in women’s hormones, particularly estrogen, as women aged, yet actual women often failed to fit that neat model. During perimenopause, hormones do not simply decline; they fluctuate unpredictably, and these fluctuations can provoke symptoms in many women. To make women’s bodies controllable and predictable—to make them fit a particular model of orderly changes—doctors and scientists joined forces. As the sociologist of science Susan Bell argues, at first surgeons simply removed women’s ovaries when they got to their forties, past childbearing age. After cutting out the ovaries, doctors could then replace the natural estrogens with precise, regulated levels of hormones, so that an unpredictable variation could be transformed into order.<sup>9</sup> Surgery and hormone synthesis appeared to give doctors the tools to regulate the internal ecologies of female hormonal systems.

Doctors soon realized that they did not actually need to do ovariectomies—they could give hormones to smooth out and rationalize the variations in a woman’s body.<sup>10</sup> The problem was that biological hormones were expensive, short-acting, and were ineffective when taken orally, because they were quickly broken down in the stomach. A search for a cheap, synthetic estrogen intensified during the 1930s.

An English biochemist named Edward Charles Dodds was at the forefront of this work. Dodds was fascinated by the close structural similarities between estrone (a form of estrogen in women's bodies), and a group of carcinogens named the "phenanthrene group." As early as January 1933, having studied the chemical properties of ovarian hormones, Dodds had foreseen that synthetic compounds could indeed act like estrogens, writing, "it seems likely that a whole group of substances of related chemical constitution will be found to have estrus-exciting properties." Dodds then turned to other compounds of similar structure, and in 1938 showed that a newly synthesized compound, diethylstilbestrol, or DES, was extraordinarily estrogenic—three times more so than natural estrogens.<sup>11</sup> After Dodd's discovery (which he never patented), DES was manufactured quite cheaply from coal tar derivatives. In 1939, within a year of Dodd's discovery, American pharmaceutical companies were submitting New Drug Applications (NDAs) to the FDA for approval of DES to treat the symptoms of menopause.

## REGULATING DES

THE FDA HAD OBTAINED authority to require that drugs be demonstrated to be safe only in 1938, after a five-year political battle, and DES was its first controversial test case. Regulators had good reason to be extremely careful about how they proceeded with this new and contested authority, because little consensus existed over the right of the federal government to regulate industry in order to protect public health, much less the environment.<sup>12</sup>

Many pharmaceutical companies now being sued by the children and grandchildren of women who took DES have argued that DES was approved because nobody suspected the chemicals might be unsafe. The financial implications that flow from this argument are powerful, since if this argument is supported by historical evidence, the drug companies can claim that they bear little liability for the harm that resulted. The archival evidence, however, refutes this argument. Before approving DES, the FDA requested that one of the leading pharmaceutical companies applying for DES approval, Merck, collate all European and American studies on the chemical.<sup>13</sup> The fact that the pharmaceutical companies prepared this document shows that the research collected within was known to the industry as well as to the regulators.

Nearly all of the DES studies had been conducted in laboratory animals, and nearly all of the results indicated that DES was more estrogenic than natural estrogens, but it did not function in the body in simple or predictable ways. DES was not metabolized by the body in the same way that natural estrogens were, and so remained potent, unlike natural estrogens, which were quickly broken down. DES remained estrogenic even when excreted from the body—the feces from treated experimental animals could induce uterine growth in mice. DES given to pregnant rats and mice and chickens led to changes in sexual differentiation in their developing offspring, and many of these deformities were not observable at birth, but only emerged when the offspring reached the age of sexual maturity. Moreover, DES increased the likelihood of reproductive cancers in those offspring when they reached sexual maturity. DES damaged the thyroid and the pituitary

gland in laboratory animals, and was linked to uterine cancer in several animal studies. In some species, DES acted as an abortifacient, increasing the risk of miscarriage. Low doses were often more toxic than high doses, a finding that particularly puzzled researchers, for it seemed to violate the emerging toxicological principle that “the dose makes the poison.”<sup>14</sup>

FDA regulators were extremely troubled by these research findings, even though little consensus existed on their applicability to humans. New Drug Chief James Durrett was particularly suspicious of DES, and very skeptical that it could ever be used safely. Beginning in 1939, as soon as the NDAs were submitted, Durrett visited numerous scientists to gather their opinions about DES, and he sent a squadron of FDA bureaucrats around the country to interview scientists known to be hostile to estrogen treatments.

Durrett found no shortage of these scientists, and he collected extensive interviews with them. Some researchers were concerned that DES seemed more toxic at low doses than at high doses. Others were perturbed by the observation that DES was not metabolized by the body, while natural estrogens were quickly broken down and removed from the body. For example, in 1939 the researchers Bernhard Zondek and Felix Sulman showed that DES, unlike natural estrogens, was not broken down in the body “in contrast to oestrone, stilboestrol is only rendered inactive in the organism to a small extent ... The fact that the organism is unable to inactivate considerable amounts of stilbestrol probably helps to explain its eventual toxic activity (compared with oestrone) particularly if large doses are used.”<sup>15</sup>

The potential for DES to cause cancer was a particular focus of FDA concern. DES emerged during a larger debate in the 1930s about the potentially carcinogenic effects of estrogens (even the body’s own estrogens). Like many endocrinologists of the era, Dodds recognized a key similarity between estrogens and synthetic carcinogens: both made cells replicate rapidly. In 1933, Dodd wrote to the journal *Nature* that “because cell proliferation which characterizes the estrus state is in some respects reminiscent of the early stages of a malignant growth, we have sought a correlation between substances having estrogenic action and those having carcinogenic properties.”<sup>16</sup> By 1939, nearly all researchers agreed that natural estrogens had the potential to be carcinogenic in laboratory animals, and that DES was at least as carcinogenic, if not more so, because it was more potent at exciting estrogenic effects.

What this meant for women, however, was uncertain. Experimental biologists tended to argue that animal studies on cancer initiation suggested women would respond in similar ways. Clinicians, on the other hand, tended to dismiss animal studies, arguing that if the women they treated with estrogens did not immediately develop cancer, estrogens must be safe. Yet when clinicians treated women with supplemental estrogens and those women did eventually develop cancer, those same doctors dismissed the women’s conviction that the drugs had caused the cancer as mere hysteria.<sup>17</sup>

Everyone wondered: If the body’s own hormones could be carcinogenic, why did not all women get cancer? While many clinicians scoffed at the possibility

that a natural substance produced by the body might induce cancer, the FDA corresponded with researchers who were concerned that, if natural estrogens were indeed carcinogenic, most women were likely to have ways of detoxifying the harmful effects of their own natural estrogens. Those mechanisms might not work against a synthetic estrogen such as DES, making them more likely to induce cancer than the natural estrogens.<sup>18</sup>

Durrett gathered material on estrogens from scientists and clinicians across the country, and he used that material to challenge industry claims to DES safety. Each time a drug company said DES was less toxic than natural estrogens, Durrett found a researcher who would give laboratory evidence to refute that claim. Each time a drug company neglected to mention a study showing toxicity, Durrett wrote back to the head of the company, reminding him that those studies existed and asking why they were not included in the submission packages. Each time a drug company submitted studies performed by the subset of researchers that were quite favorable to DES, Durrett pointed out that other researchers had a very different perspective. Each time an industry representative insisted that animal studies had little meaning for human subjects, Durrett found scientists who disagreed.<sup>19</sup>

In memos written during 1939 and 1940, Durrett and Walter Campbell, commissioner of the FDA, insisted that they were obliged to follow what they called “the conservative principle.” Such a principle assumed that if evidence were not available that showed clear absence of harm, a prudent regulator would assume harm might exist. This, of course, is similar to what is known today as the “precautionary principle.” For example, when one DES manufacturer accused Campbell of being “unscientific” for slowing the approval of DES within the FDA, Campbell wrote back: “In your letter of July 23 you indicate that one or more physicians do not believe that there is definite proof that estrogenic substances will cause cancer. We are aware that all physicians are not equally impressed with the evidence that estrogenic substances may induce cancer under certain conditions. However, in view of the very serious and often fatal nature of cancer, we believe that a conservative view point on this question is wholly warranted.”<sup>20</sup>

Given the absence of strong evidence that DES was safe, and given the scientific uncertainty over its mechanisms of action and metabolism, Durrett urged Campbell to refuse to approve DES—not because he had any proof that the drug would harm women, but because he had no proof the drug would *not* harm women.<sup>21</sup> Campbell followed Durrett’s advice, and in 1940, the FDA told the companies in 1940 to withdraw their NDAs for the approval of DES. Campbell noted that this decision was not final, and the drug companies would be allowed to resubmit if they could gather sufficient evidence showing DES to be safe in women.

The pharmaceutical companies withdrew their individual applications from the FDA and decided to pool their resources, forming a group known as the “Small Committee” that would attempt to reverse the initial FDA rejection of DES. The Small Committee, led by officials from Eli Lilly, Winthrop, Upjohn, and Squibb, created what they called the Master File, a collection of clinical evidence supporting their claims to the safety of DES. The Small Committee controlled the contents of the Master File by excluding all animal studies and including



evidence only from short-term clinical studies. The historians Richard Gillam and Barton Bernstein argue that the Small Committee “thus effectively excluded unnerving evidence ... based upon laboratory work with animals. As a result, a number of risks simply disappeared from sight.”<sup>22</sup>

The drug companies also hired a lobbyist named Carson Frailey, the executive vice president of the American Drug Manufacturers Association. To generate evidence that DES was safe for women, Frailey worked with the drug companies to supply hundreds of doctors with samples to give to their female patients, thus creating a market for the drug even before approval, and political pressure to aid approval. These doctors treated thousands of patients with DES, and many of these doctors and patients then wrote both to the FDA and to politicians (including President Franklin Delano Roosevelt), asking them to speed the approval of DES.<sup>23</sup> Frailey persuaded fifty-four doctors from around the country to write to the FDA, describing their clinical experiences with a total of more than five thousand patients. Only four of these fifty-four doctors felt that DES should not be approved, and the result was that, against the concerns of many of the FDA medical staff, the FDA’s drug chief Theodore Klumpp recommended that the FDA approve DES.<sup>24</sup>

In 1940, FDA staff had used scientific uncertainty as a justification for refusing to approve DES, but that strategy was not strong enough to resist court challenges and political pressures. The applicability of animal experiments to human safety was particularly contentious. After animal experiments on pesticide residues in the late 1930s showed that residues could be quite toxic, fruit growers had lobbied to prevent the FDA from using results from animal studies to determine risks to people. These political pressures resulted in a loss for the FDA in 1937, when a rider to the appropriation bill forbade the use of FDA funds to conduct laboratory animal investigations to determine the effects of insecticides on human health.<sup>25</sup> Yet the FDA’s Division of Toxicology was eager to refine animal toxicity testing, and Jack Curtis, the chief pharmacologist of the FDA, was concerned enough by DES to urge that long-term studies in primates needed to be done to understand potential carcinogenicity before the drug could be made available for human use.<sup>26</sup>

A federal court decision against the American Medical Association (AMA) made the FDA wary of engaging with drug companies over the issues of scientific uncertainty—particularly the applicability of animal models to humans—as justification for stiff regulations on estrogens. In the late 1930s, a company named Hiresta had marketed an breast-enlarging estrogen cream. The AMA had been concerned enough about a possible increase in cancer risk from topical estrogen that they published an editorial decrying the dangers of this cream, and Hiresta sued them for defamation. The FDA used animal studies to support the AMA’s argument that estrogens were known carcinogens. The federal judge ruled against the AMA, arguing that animal studies failed to prove that estrogen cream would definitely lead to cancer in women—and that clear proof of actual harm to specific women was lacking. This court case led the FDA to abandon its planned campaign to regulate estrogen breast creams and made them wary of continuing to use animal studies in their case against new drug applications for DES.<sup>27</sup>



After this court case, the FDA leadership decided to deal with scientific uncertainty with a compromise, allowing the drug to be available only with a prescription—a novel idea at the time—while requiring elaborate warnings about possible toxic and carcinogenic effects. Yet because they did not trust patients, particularly female patients, to judge medical information, regulators within the FDA insisted that these warnings be made available only on a separate circular that patients would not see. Doctors could get this warning circular only by writing to the drug companies and requesting it. Letters between companies and FDA regulators reveal that both groups feared that if a woman ever saw how many potential risks DES might present, she might refuse to take the drug—or else she might sue the company and the prescribing doctors if she did get cancer or liver damage after taking the drug. Since most doctors were unwilling to write off for a special circular before prescribing a heavily promoted drug, the distrust of female patients meant that few clinicians and fewer patients ever had any idea that the drug was toxic. The compromise solution foundered on its assumptions about women's untrustworthiness as patients.<sup>28</sup>

In 1941, the FDA insisted that the drug was absolutely contraindicated for pregnant women because of possible risks to the uterus (not to the fetus), and that women who wished to retain their fertility should also never take DES.<sup>29</sup> For the FDA, DES was a toxic substance that needed to be strictly regulated, and officials hoped that clearly defined limits on its use would allow them to control the substance while sidestepping political pressures. Within a year, however, the FDA realized that enforcement of its initial limits on DES use was not going to be easy. One company began selling DES over the counter, in direct violation of law. Lawyers in the General Counsel's office decided not to prosecute, informing surprised FDA staffers that they wanted the first test case in court of the FDA's new regulatory authority to be over a drug with uncontestable public harm.<sup>30</sup> The effect on the FDA was predictable. As drug companies learned that the government was not willing or able to enforce regulations against the new drug, they overwhelmed federal staffers with a deluge of more than one hundred new drug applications for various DES formulations and claims. Several years later, in 1945, the FDA allowed drug companies to drop the warning that DES was potent and dangerous and allowed a multitude of new uses, including use in pregnancy.<sup>31</sup>

Starting in 1939, a physician named Dr. Karl John Karnaky of Houston began experimenting with the use of DES in pregnant women, and he soon became an enthusiastic promoter of DES for all pregnancies. As he later recalled, "The drug companies came to Houston, ... fed me and dined me ... and I started using it."<sup>32</sup> One of his research reports described experiments done on fourteen "normal" pregnant women in his privately financed clinic, experiments that included repeated X-rays and injections with up to 24,000 mg of diethylstilbestrol. He noted that "all babies in the study were found to be entirely normal," even though he followed only five patients to term. He did observe that all five babies "exhibited a darkening of the areolae around their nipples, labia, and linea albae, similar in intensity to that of their mothers, indicating that this effect of diethylstilbestrol also is shared by the fetus."<sup>33</sup> Although drug companies have insisted that no

researcher suspected DES could cross the placental barrier and affect the fetus, this study, which the companies cited as evidence of DES's safety, shows evidence of the opposite.

Research in the early 1940s by the physicians Priscilla White, George Smith, and Olive Smith encouraged the hope that DES might help to prevent miscarriages. The Smiths, researchers at Harvard Medical School, theorized that because elevated estrogen levels during pregnancy stimulate progesterone, necessary for the uterus to sustain a pregnancy, failures of pregnancy might be due to low levels of estrogen and thus treatable by DES. Other researchers were dubious, and a lively debate arose in the medical literature about the safety and efficacy of these experiments. Yet given the prestige of Harvard, and the influence of the *American Journal of Obstetrics and Gynecology* where the early results were published, many physicians convinced themselves that DES was indeed a miracle drug for stopping "accidents of pregnancy."<sup>34</sup>

Drug companies lobbied the FDA intensely to approve the drug for pregnancy, sending samples to doctors to create a consumer market for the drug, overwhelming the FDA with short-term data on human effects and ignoring data on animal experiments, and complaining incessantly about the safety limits constructed by the FDA. For example, Squibb sent twelve physicians (including Karnaky) free samples of DES to give to pregnant women, so that Squibb could present evidence of safety to the FDA. Of these twelve doctors that were given DES by Squibb, only eight doctors' records were actually submitted to the FDA, containing records of 108 pregnancies. Outcomes were described for sixteen pregnancies; the other ninety-six pregnancies were not followed to term. Of the sixteen pregnancies that were followed, nine pregnancies resulted in full-term, healthy babies, three pregnancies ended with premature births, and four babies were stillborn. In other words, 43.75 percent of pregnancies treated with DES had adverse outcomes at birth. A full quarter of them ended in still births, and it is not known what happened to the surviving children when they reached puberty.

Many things are troubling about these studies, from the lack of controls (which were expected practice in clinical research by the late 1930s), to the insistence of researchers on seeing what they wanted to see. For example, one patient was given 69,025 mg of DES over twenty-six weeks of her pregnancy. She began bleeding during her eighth month and had a premature birth, which suggests DES did not work for her, even though the doctor interpreted this result as a success, assuming that she should have lost her child without DES. Another doctor wrote of a premature birth on DES treatment: "P.S.: the fourth case delivered today. ... She started in labor spontaneously delivering a premature baby of 5 lbs., which we felt was about 36 weeks gestation. She been taking 100 mg stilbestrol daily. The cause of the ruptured membrane, I am sure, was due to excessive shopping."<sup>35</sup> Attributing a premature birth to "excessive shopping" rather than to the doctor's own experiments, is troubling enough, but what is even more surprising is that the FDA was willing to accept these results as evidence of DES's safety for fetuses.

Studies in the late 1930s had shown that in certain animal species, DES was actually an abortifacient. DES, given to pregnant rats and mice and chickens, led

to changes in sexual differentiation in their developing offspring, and many of these deformities were not observable at birth, but only emerged when the offspring reached the age of sexual maturity. Moreover, DES increased the likelihood of reproductive cancers in those offspring when they reached sexual maturity.<sup>36</sup> These studies were known to both the drug companies and to the FDA, for the companies collated their abstracts into a document that they submitted to the FDA in 1940.<sup>37</sup> These animal studies played a significant role in the FDA's initial 1940 decision to reject the DES application for use in menopause. Yet the puzzling thing is that they were completely overlooked in the 1947 FDA decision to allow DES during pregnancy. No mention is made of them in the NDAs submitted by the drug companies, and the FDA did not mention them either in any of the approval documentation or the extensive memorandums between staffers discussing status of the approval requests.<sup>38</sup>

Nor did the FDA or the drug companies mention the burgeoning evidence published since DES approval in 1941 that showed DES's ability to cross the placenta and to cause abortions in non-human animals—and potentially in humans as well. One researcher warned in 1944 that sex hormones known to alter fetal development of animals probably did the same in humans.<sup>39</sup> In a 1947 article later cited by a few drug companies in their NDAs, two researchers expressed concern that DES might “affect the glandular balance of the child in utero.”<sup>40</sup>

In 1947, the FDA approved DES for pregnant women with diabetes, and almost immediately, widespread use of DES in *all* pregnancies began. In 1953 and 1958 two reviews of the available research showed that DES actually increased the risk of miscarriages—even though it was supposed to be decreasing miscarriages.<sup>41</sup> Nevertheless, drug companies advertised the drug intensively, urging doctors to prescribe it even for normal women “to make a normal pregnancy more normal.” By 1957 the *Journal of Obstetrics and Gynecology* recommended it for all women to produce bigger and stronger babies.<sup>42</sup>

Meanwhile, millions of people were being exposed to DES through their diet. Beginning in the 1947, DES was approved in the United States as a growth-promoter, first in poultry, then in hogs and cattle.<sup>43</sup> Very high levels of DES were soon detected in poultry sold for human consumption—up to one hundred times the concentrations necessary to cause breast cancer in mice. Concern over DES effects soon grew in various lay groups: women who used the drug, farmers who handled treated livestock, and workers who manufactured the material. Women who were treated with DES for menopause began to be concerned about painful breasts, uterine bleeding, and the possibility of breast cancer. When these women wrote to the FDA, their concerns were dismissed as hysterical.<sup>44</sup> Mink farmers who were feeding their animals discarded chicken heads that contained DES implants began to notice that their mink were having miscarriages. The FDA refused to investigate, arguing that farmers were entirely unqualified to observe, much less interpret, hormonal problems. When the owner of Arapahoe Chemicals wrote to the FDA in 1947, concerned that male workers who handled DES were suffering impotence and breast growth, the FDA advised them to hire old men who might be less concerned about DES's “devirilizing effect.”<sup>45</sup> While this was

clearly not the FDA's finest hour, the responses indicate more than simple negligence. A deeper anxiety about lay challenges to the authority of physicians, scientists, and regulators was embedded in these responses.

Finally, after exposed male agricultural workers suffered sterility, impotence, and breast growth, the FDA banned its use in chickens in 1959, while allowing its use in cattle feed to continue, and allowing it to be promoted as a wonder drug for pregnancy. In 1971, researchers in Boston noticed a cluster of extremely rare vaginal cancers in young women whose mothers had taken DES while they were pregnant. DES mothers and children organized to call for a research effort.

The full dimensions of the health and environmental disaster that resulted are only now becoming apparent. By 2002, DES had emerged in toxicological studies as a model carcinogen and developmental disruptor, meaning that the developmental toxicity of other chemicals is usually measured against DES.<sup>46</sup> Of the 2 million to 5 million children who were exposed to DES prenatally, nearly 95 percent of them have experienced reproductive tract problems, including menstrual irregularities, infertility, and higher risks of a variety of reproductive cancers.<sup>47</sup> At the peak of its use in the 1960s, DES was given to nearly 95 percent of feedlot cattle in America, which meant millions of people consumed meat tainted with the artificial estrogen, and the estrogenic wastes from feedlots made their ways into aquatic ecosystems, with unknown effects.

MULTIPLE HYPOTHESES have been proposed to explain how the DES disaster could have unfolded. As described above, many drug companies argue that DES was approved because of the limits of knowledge—nobody suspected the chemical might cause harm. The archival evidence refutes this argument, because not only did numerous studies exist showing the potential for harm, the drug companies were clearly aware of these studies, having collated them for the FDA.

A variant on this argument is presented by the physicians Roberta Apfel and Susan Fisher, who argue that the tragedy was an inevitable outcome of the state of 1940s medical research.<sup>48</sup> Doctors and researchers were well-meaning, but they had no way of suspecting the limitations in the clinical research on DES. Yet the need for controls in clinical research was widely accepted by the early 1940s, and many medical researchers, pharmacologists, and regulators were troubled by research on DES. That concern did not get translated into policy, but limited medical knowledge was not the major reason why.

The historians Richard Gillam and Barton Bernstein have argued that the tragedy arose because the FDA worked hand in hand with the industry, reneging on their responsibilities as regulators. They write: "Put bluntly, FDA officials were predisposed, even eager, to approve the drug for human use, and such approval required a special effort—by no means inevitable—to accomplish this intended purpose."<sup>49</sup> This argument ignores the FDA's initial decision to reject DES and the intense scrutiny the DES applications received from FDA staff. By the mid-1950s, the FDA was weakened, demoralized, and unwilling to stand up to industry. But this was not the case during the debates over DES in the late 1930s and early 1940s, when the FDA staff and commissioner were still skeptical about claims

made by drug companies.<sup>50</sup> Political pressures played an important role in the outcome, but not because the FDA was merely a pawn of the industry.

Other scholars argue that sexism explains DES. The journalist Barbara Seaman writes that DES reveals the arrogance of male doctors and scientists experimenting on women as if they were little more than experimental animals. American studies scholar Julie Sze locates the reasons for acceptance of DES in gendered conceptions of women's roles as bearers of children, combined with "a utopian belief that technologies could harness and 'improve' on nature itself." DES was considered benign because it was making a "natural," "biological," and "normal" process more effective.<sup>51</sup> Widespread enthusiasm for children in the postwar years, combined with the frustration of the medical community that they had been so powerless to decrease miscarriages, helped to persuade much of the medical community that this convenient regimen of pills could save babies.<sup>52</sup>

The comment about "excessive shopping" being the true cause of an adverse pregnancy outcome suggests that gender assumptions were embedded in DES research and approval, but sexism is not the entire story.<sup>53</sup> While gender assumptions helped define menopause and pregnancy as diseases in need of medical treatment, and beliefs about gender shaped certain policy failures such as decisions about warning circulars and refusal to investigate personal accounts of harm, sexism alone cannot explain why the FDA staff approved DES.

DES approval was influenced by changing conceptual models that made it difficult for scientists, doctors, and regulators to counter drug company arguments in favor of DES, even when the regulators were presented with growing evidence of toxicity. The pharmaceutical companies used several strategies to buttress their case for DES. First, the industry manipulated the concept of naturalness, with its attendant implications of purity and safety. The drug companies argued that since bodies naturally produced estrogens, DES was similar to nature and therefore safe as well. For example, Lilly submitted a statement on its required warning circular that reassured doctors that "in toxicological studies stilbestrol resembles the natural estrogens. ... In terms of the estrous dose Geschickter has reported stilbestrol to be no more carcinogenic than the natural hormones in the rat."<sup>54</sup> Because the warning did not go on to detail the evidence that shows natural hormones can be carcinogenic, the statement implied that DES would not cause cancer.

The second conceptual strategy the drug companies used to argue for approval of DES relied on assumptions about human exceptionalism, and particularly on the uncertainty about the applicability of animal models to humans. The drug companies simply insisted that animal studies could be ignored, if human short-term studies showed no harm. FDA administrators did not agree with this insistence that humans were different from other animals, yet as the Hiresta case shows, FDA staff knew that their concerns about DES were not supported by evidence that would stand up to court challenges.

While FDA regulators were skeptical about the drug companies' arguments about naturalness and human exceptionalism, both drug companies and regulators shared certain conceptual frameworks that made it difficult for them

to interpret growing evidence of fetal toxicity. The medical historian Ann Dally argues that, before the thalidomide crisis in the 1960s, many scientists and doctors assumed the womb was inviolate and could not be affected by outside world. Most doctors and scientists believed that the placenta provided a barrier to the outside world. Even though increasing toxicological research in the 1940s showed that estrogens could cross the placenta, most physicians continued to believe the placenta protected the fetus from harm. Dally suggests that “belief in the placenta as a perfect barrier against damaging influences in the environment was reinforced by the Victorian tendency to put ‘woman’ on a pedestal, which led to idealisation of the womb as well as of the woman.”<sup>55</sup> This belief also reflected available technology: until the invention of ultrasound in the 1970s, the fetus was hidden in the womb. People could not visualize the development of the fetus, so it was easy to assume the fetal environment was separate.<sup>56</sup>

In 1962, when thalidomide had profound effects on fetal development, the medical community began to accept that drugs could indeed cross the placenta. Nevertheless, it was not immediately apparent to anyone—even Frances Kelsey, the FDA medical officer who had refused to approve thalidomide—that thalidomide had implications for DES. Thalidomide produced immediate, massive birth defects, while no birth defects were initially apparent with DES. Even though reports were appearing in the technical literature about apparent intersex conditions in children exposed to DES *in utero*, few doctors could comprehend that a hormone given during pregnancy might have effects that would only emerge decades later.<sup>57</sup>

Conceptual models in embryology also help explain why doctors and regulators discounted evidence of DES toxicity to the fetus. Ecological concerns had played a major role in the development of embryology in the late nineteenth century, as investigators tried to understand how the environment shaped development of embryos. This changed in the early twentieth century, as a reductionist paradigm of development replaced the ecological paradigm. Scientists increasingly downplayed the role of the environment in development when social and technological forces made embryonic development easier to study internally than externally. By the 1940s, most developmental biologists had adopted a belief that the fetus was essentially determined by the genome, therefore invulnerable to influences from the environment. As the developmental biologist and historian of science Scott Gilbert writes: “genetics brought a new form of preformationism. Instead of a dynamically acting organism taking its cues from the environmental conditions and from the way that cells interact with each cell division, the 20<sup>th</sup> century brought a dominant and popular view that has often emphasized genes as programmed to carry the information of heredity, which was also the information necessary to construct an individual.”<sup>58</sup>

Conceptual models about the links between bodies and environments extended beyond embryology into wider spheres of health, and these models also influenced the regulation of DES. Linda Nash, in *Inescapable Ecologies*, shows how the transition from an ecological view of health to a germ-theory of health in the late nineteenth century helped create a belief that bodies were impermeable to the



environment. Mechanistic, reductionist views of toxicology and health pushed aside beliefs that assumed bodies existed in complex relations with their environments, where the health of the environment could influence the health of the body. Yet, as Nash shows, many public health workers did not completely abandon ecological views of health, and the FDA regulators were no exception.<sup>59</sup>

The classic foundation of mechanistic toxicology is that “the dose makes the poison”—that drugs behave in simple linear fashions, so high doses might be dangerous, but eventually you can find a dose small enough to be safe. From this model, drug companies argued that, because the body can survive high doses of its own estrogen in early pregnancy, supplemental doses of estrogen that were lower than the body’s own pregnancy surges must be safe. Because bodies naturally produced estrogens, low levels of additional estrogens should not have a toxic effect, if those additional estrogens were just a fraction of the highest levels of natural estrogens.

The U.S. government continues to allow synthetic hormones in livestock because of these same arguments: the chemicals are natural (or very close to natural), so they must not be a problem, and supplemental doses must not be a problem because natural levels are sometimes high.<sup>60</sup> Yet as early as the 1930s, FDA staff noted numerous ways that synthetic hormones did not follow mechanistic models. For example, DES induced cancer at low doses but not higher doses, and DES harmed the thyroid, and DES remained estrogenic in the feces from treated animals. These results raised concern within the FDA, but without an alternate model of hormones and health, they became a collection of odd results that could easily be discounted.

One of the puzzles of estrogens—as Durrett and other FDA staff of the 1930s recognized—is that they do not behave mechanistically. A high dose of estrogen at certain times in a woman’s life can be protective against cancer, while tiny doses at other times can induce cancer. For example, the low doses of estrogen present in hormone replacement therapy appear to increase breast cancer risk in some populations of menopausal women, while the very high doses of hormones present in pregnancy can be protective against breast cancer, if a girl has her first pregnancy when she is very young.<sup>61</sup> No simple cause-and-effect mechanism exists between estrogen exposure and cancer development, but rather a complex ecosystem of feedback loops, estrogen receptors, and exchanges within the body.

Ecological models of health envision the body as permeable to the environment. As René Dubos argued decades ago, health can be viewed ecologically not as the simple absence of disease, but rather as “the ability to adapt to new or changing circumstances; compromised health may become apparent only when new sources of stresses are applied and the individual fails to adapt.” Health consists of a “complex set of adaptations to stress, feedback loops, pathways of nutrients and energy, flows of energy and waste, and regulatory mechanisms that constrain these pathways.”<sup>62</sup> In this model, endocrine disruptors such as DES are not of concern merely because they have potential to harm the body, for bodies are constantly negotiating exposures to substances that have the potential to cause harm. The disturbing thing is that endocrine disruptors

transform the body's ecological repair mechanisms, often at the biochemical level. In particular they alter the epigenetic processes that link environment and gene, leading to changes in gene expression, and in turn to changes in the numbers and types of immune cells in the blood, and changes in hormone production and metabolism. They alter ecological processes of human health, just as they alter broader ecosystem processes.

Changing conceptual models influenced how various groups interpreted and acted on medical and scientific findings. But conceptual models alone do not explain the synthesis of factors that emerged to create the disaster. Conceptual models alone did not force the FDA to approve DES, and conceptual models alone did not force millions of women to take a new drug. FDA staff were skeptical about the drug companies' claims, but they based their skepticism on concerns that could not be defended in court and could not stand up against political pressures.

The importance of precaution when faced with uncertainty—and the difficulties of defending a precautionary principle under political pressure—is a key lesson from this history. In 1938, after a long battle, the FDA was given the regulatory power to require that drug companies show their new drugs were safe. But no one knew what safety meant. No one knew what caused cancer. No one knew what effects a synthetic hormone derived from a carcinogen might have on people. No one knew how to translate studies done on lab animals into potential risks for adult humans, much less fetuses that one day might become adults. No one knew how actual women living in complex environments might respond to new drugs. Uncertainty wreathed every aspect of this brave new world of drug technologies and regulation. Yet it was not at all inevitable that FDA's response to such uncertainty would be to side with the drug companies. The FDA initially responded with precaution and only abandoned that precaution under a constellation of political pressures for drug approval from drug companies, beliefs about women as patients and mothers, and tensions between ecological and reductionist models of health and fetal development. That retreat from precaution is at the heart of the DES tragedy.

**Nancy Langston** is professor of environmental studies and forestry at the University of Wisconsin-Madison. She is author of *Forest Dreams, Forest Nightmares: The Paradox and Old Growth in the Inland West* (Washington, 1996), and *Where Land and Water Meet: Transforming a Western Landscape* (Washington, 2006). This article is based on research for her latest book, *Toxic Bodies: An Environmental History of Endocrine Disruptors*.

## NOTES

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Department colloquium at Dartmouth College. FDA headquarters staff and staff at the National Archives and Records Center were extremely helpful with my requests for access to materials, and FOIA requests.

1. Ted Schettler, "Endocrine Disruptors: The State of the Science," Greater Boston Physicians for Social Responsibility (1997); accessed online at <http://web.archive.org/web/19990220214027/www.psr.org/tedfs.htm>.
2. For critiques of the precautionary principle, see the essays in Julian Morris, ed., *Rethinking Risk and the Precautionary Principle* (Oxford, UK: Butterworth-Heinemann, 2000).
3. Sonja Boehmer-Christiansen argues that the precautionary principle evolved out of the German concept of *Vorsorgeprinzip*, which developed in the socio-legal tradition of the 1930s democratic socialism. *Vorsorgeprinzip* centered on the concept of good household management, and the concept justified state involvement in planning of the economy, technology, morality, and social initiatives. The precautionary principle became an explicit tenet of environmental policy in West Germany during the 1970s, and in 1984 was introduced internationally at the First International Convention on the Protection of the North Sea, and has since become a central principle of consumer and environmental protection policy in the European Union. The 1992 Rio Declaration on Environmental and Development was explicitly grounded in precaution. In 1998, a group of thirty-five scientists, policy makers, and advocates concerned about evidence of endocrine disruption developed the Wingspread Statement, a consensus statement on precaution. Andrew Jordan and Timothy O'Riordan, "The Precautionary Principle in Contemporary Environmental Policy and Politics," in *Protecting Public Health and the Environment: Implementing the Precautionary Principle*, ed. Carolyn Raffensperger and Joel Tickner (Washington, DC: Island Press, 1999), 15-36. See, also, Sonja Boehmer-Christiansen, "The Precautionary Principle in Germany—Enabling Government," in *Interpreting the Precautionary Principle*, ed. Tim O'Riordan and James Cameron (London: Earthscan Publications, 1994), 3.
4. Letter, Walter Campbell, Commissioner of FDA, to Merck & Co, re NDA 4076, 11/3/41. In FDA, National Archives and Records Administration at College Park, Maryland, (hereafter NARA). RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1941. Folder 526.1 Nov-Dec.
5. For example, in several cases during 1947, the FDA argued that workers in DES manufacturing facilities who complained of sterilization and cancer had "failed to provide material proof" that DES had caused their illness, so there was no need to restrict DES: "Quantitative data are lacking. The data on carcinogenesis is meager and many published opinions are not properly backed up on the facts. I personally doubt if most or not all of the people who have raised the question have failed to provide material proof of their contention. The other side, however, has adequate proof of the lack of carcinogenic activity of the estrogen. To be on the safe side, however, I would suggest to these people that female employees be screened to eliminate any who may have a family history of carcinoma." FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1947. Folder 526.1. Handwritten notes by FDA staff on the Letter, Richard Waugh, Technical Director, Arapahoe Chemicals, Inc. to Dr. Robert Stormont, FDA. June 26, 1947. Letter was circulated within the FDA for handwritten and initialed comments.
6. For a sociological perspective on the initial DES approval process, see Susan Bell, "The Synthetic Compound Diethylstilbestrol, (DES) 1938-1941: The Social Construction of a Medical Treatment" (PhD diss., Brandeis University, 1981). An examination of DES technology is in Julie Sze, "Boundaries and Border Wars: DES, Technology, and Environmental Justice," *American Quarterly* 58 (2006): 791-814. Roberta J. Apfel and

Susan M. Fisher have examined the development of DES in *To Do No Harm: DES and the Dilemmas of Modern Medicine* (New Haven: Yale University Press, 1984). Diana Dutton's "DES and Drug Safety" chapter in her book *Worse Than the Disease: Pitfalls of Medical Progress* (Cambridge: Cambridge University Press, 1988) contains important material for understanding DES. Popular works on DES include Cynthia Laitman Orenberg, *DES: The Complete Story* (New York: St. Martin's Press, 1981); Stephen Fenichel and Lawrence S. Charfoos, *Daughters at Risk: A Personal DES History* (New York: Doubleday, 1981), and Robert Meyers, *DES: The Bitter Pill* (New York: Seaview/Putnam, 1983). For a review of the scientific literature on DES effects, see: R. M. Giusti, K. Iwamoto, and E. E. Hatch, "Diethylstilbestrol Revisited: a Review of the Long-term Health Effects," *Annals of Internal Medicine* 122 (1995): 778-88. DES in beef is examined in Sze, "Boundaries and Border Wars," and in Alan Marcus, *Cancer from Beef: DES, Federal Food Regulation, and Consumer Confidence* (Baltimore: Johns Hopkins University Press, 1994). Intersex effects on sons of DES mothers are summarized in Scott P. Kerlin, "The Presence of Gender Dysphoria, Transsexualism, and Disorders of Sexual Differentiation in Males Prenatally Exposed to Diethylstilbestrol: Initial Evidence from a 5-Year Study," paper presented at 6th Annual E-Hormone Conference New Orleans, October 27-30, 2004; accessed online at <http://www.desexposed.org/aboutdes/dessons5yrstudy.html>.

7. Nelly Oudshoorn, *Beyond the Natural Body: An Archeology of Sex Hormones* (London: Routledge, 1994), 26, 39.
8. Joanne Meyerowitz, *How Sex Changed: A History of Transsexuality in the United States* (Cambridge: Harvard University Press, 2002), and Oudshoorn, *Beyond the Natural Body*.
9. Bell, "The Synthetic Compound Diethylstilbestrol," 15 ff.
10. As one researcher on DES, Dr. Edward Davis, stated in an interview with the FDA in 1940, the point of DES was to control natural fluctuation in hormones. "The essential treatment for the alleviation of menopausal symptoms ... was to administer 1 milligram of Stilbestrol orally each day for a period of three months; then to decrease the dosage to 1/2 milligram per day for three months, followed by 1/2 milligram every other day for three months, and finally 1/2 milligram two times a week for three to six months. If the drug is discontinued too soon, symptoms will recur. Dr. Davis aims by this method of treatment to gradually decrease the amount of estrogenic substance in the body and believes by this matter to be able to avoid the symptoms which are so common at the menopause." Memorandum of interview. Dr. M. Edward Davis, University of Chicago, and Dr. Ernest Q. King, Medical Officer of the FDA. Nov. 1, 1940. in FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1940. Folder 526.1-11.
11. See the review in E. C. Dodds et al., "Synthetic Oestrogenic Compounds Related to Stilbene and Diphenylethane. Part 1." *Proceedings of the Royal Society of London. Series B, Biological Sciences* 127 (1939): 140-67. See, also, E. C. Dodds et al., "Oestrogenic Activity of Certain Synthetic Compounds," *Nature* 141 (1938): 247-49.
12. Thanks to an anonymous reviewer for suggesting this perspective. Philip Hilts, in *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Knopf, 2003), 72-107, explores the controversies over the regulatory power of the FDA. Bell notes that "The medical science represented by the production of DES involved negotiations among clinical investigators, officials at the FDA, and pharmaceutical manufacturers over how to judge DES, as well as whether it was safe prior to its release for sale. DES was not the first drug to be reviewed after the passage of the 1938 Act. However, it was the first drug that was not life saving and possibly unsafe. In addition, more drug manufacturers submitted applications to market DES than for any other drug up to that time. Thus, it was used by FDA officials as an occasion to clarify procedures and to set policy for future cases." Susan Bell, "Gendered Medical Science: Producing a Drug For Women," *Feminist Studies*, 21 (1995): 469-500.

13. These studies were included in the annotated bibliography prepared by Merck and Co., April 1941, submitted to the FDA. *Stilbestrol (Diethylstilbestrol): Annotated Bibliography* (Rahway, NJ: Merck and Co., Inc., April 1941).
14. R. L. Noble, in October 14, 1938, published a study titled "Functional Impairment of the Anterior Pituitary Gland Produced by the Synthetic Oestrogenic Substance 4:4' Dihydroxy-[alpha: beta]-diethylstilbene," *Journal of Physiology* 94 (1938): 177-83.
15. Bernhard Zondek and Felix Sulman wrote, "While after absorption the hormone esters are rapidly rendered inactive in the organism, this is not the case with stilboestrol. In the excreta large amounts of the active substance are found. The fact that the organism is unable to inactivate considerable amounts of stilboestrol probably helps to explain its eventual toxicity (compared with oestrone)." Cited in *Stilbestrol (Diethylstilbestrol): Annotated Bibliography*, 10.
16. Deborah Cadbury, *Altering Eden: The Feminization of Nature* (New York: St Martin's Press, 1999), postscript. See E. C. Dodds and W. Lawson, "Synthetic Estrogenic Agents without the Phenanthrene Nucleus," *Nature* 137 (1936): 996; and E. C. Dodds and W. Lawson, "Molecular Structure in Relation to Oestrogenic Activity: Compounds without a Phenanthrene Nucleus," *Proceedings of the Royal Society. London B* 125 (1938): 222-32.
17. FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1940. Folder 526.1-.11. Memorandum of interview. Dr. U. J. Salmon (NY) and Dr. Gordon A. Granger, Medical Officer of the FDA. July 13, 1940.

A doctor reported that the wife of another doctor in his practice had developed breast cancer after being treated with estrogens derived from horse urine. She was described as having "gone crazy" when she learned she had breast cancer after "receiving estrogens over a long period of time for premenstrual headaches and later on had received them for the menopause. There was no way to determine with any degree of accuracy the amounts she had received because so many people had been involved in the administration. Both he and Dr. Duke had administered various preparations in various strengths both by hypodermic and by mouth." Kohn went on to dismiss the possibility that these supplemental estrogens could have been linked to Mrs. Duke's breast cancer, on the grounds that "Mrs. Duke had a carcinoma background since her mother had died of a malignancy." He added that "in spite of Mrs. Duke's experience, he had no qualms about administered estrogens. ... he then said he thought the Administration was going too far in the warning and caution direction." FDA, National Archives and Records Administration at College Park, Maryland. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1940. Folder 526.1-.11. Memorandum of interview. Dr. C. Kohn, Kansas City, MO, and Dr. Gordon A. Granger, Medical Officer of the FDA. July 26, 1940.

18. Dr. William Stoner wrote to James Durrett that while all estrogens were problematic, synthetic ones were likely to be even worse, because they were novel substances in evolution: "It was stated that the mammalian organism has become accustomed to the action of certain hormones which may produce damage although they usually do not, while other substances having actions simulating those of the natural hormones, such as synthaline, dinitrophenol, stilbestrol, etc., more or less uniformly cause damage with which the organism has not learned to cope." FDA, FIO. DES Microfiche # 166. Folder 159. Letter, Dr. William H. Stoner, Medical Research Division, Schering Corporation, to James Durrett, FDA. July 6, 1939.
19. For example, in January 1940 the FDA sent out a press release to the *Science News Letter* stating that stilbestrol was "effective but potentially dangerous," citing the American Medical Association and its Council on Pharmacy as authorities. The press release warned that "Liver damage and cancer are among the possible dangers seen in use of the new synthetic hormone. The medical profession in general is advised not to use it until further studies have been made by experts ... because these products have proved



- cancer-inducing in animals." Press clipping from *Science News Letter*, January 13, 1940. "Synthetic female hormone pills considered potential danger," in FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1940. Folder 526.1-13.
20. Letter, W. G. Campbell, Commissioner, to Mr. Charles Dunn, NYC, July 1940 (full date unreadable in microfilm). FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1940. Folder 526.1-32. Another researcher interviewed by the FDA staff, Dr. I. Penchars, "pointed out that he did not know what the dangerous dose of estrogen was nor did he know what a safe dose of estrogen was nor did he know how to find out. He pointed out that with our state of knowledge in this condition, it was inadvisable to permit such a product to be part of a cosmetic used for indiscriminate distribution." Memorandum of interview (follicular hormone in cosmetics. Dr. Hans Lisser, Dr. I. Penchars, Dr. Allen Palmer, Dr. I. Perry (San Francisco), with Dr. R. W. Weilerstein of FDA. Sept. 3, 1940. In FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1940. Folder 526.1-13.
  21. As FDA Commissioner Walter Campbell wrote in a letter to Merck: "In conclusion it might be well to again state that the main reason for the suggested revision of this sentence is conservatism, and in our judgment the public interest may well be served by the exercise of conservatism with respect to this drug at this time." Letter, W. G. Campbell, Commissioner of FDA, to Merck & Co., re NDA 4076, 11/3/41. In FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1941. Folder 526.1 Nov-Dec.
  22. Richard Gillam and Barton J. Bernstein, "Doing Harm: The DES Tragedy and Modern American Medicine," *The Public Historian* 9 (Winter 1987): 57-82.
  23. For example, in one interview, James Durrett wrote: "Dr. Nelson then took a bottle of 1 mgm Stilboestrol Tablets (Burroughs & Welcome) from his desk and asked for information concerning the preparation. He said Burroughs & Welcome has sent them to him and requested a clinical trial." Memorandum of interview. Dr. Harry M. Nelson, Detroit, and Dr. Gordon A. Granger, Medical Officer of the FDA. 1/19/40. In FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1940. Folder 525.03-526.

A woman named Agnes Sullivan wrote to President Franklin Roosevelt demanding that DES be made available; James Durrett wrote back to Sullivan: "Your recent letter addressed to President Roosevelt has been referred to this Administration for consideration and reply." Durrett went on to add that DES was not available because "it has not been sufficiently investigated by experts to show that it is safe for use." FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1940. Folder 526.1-32. Letter, J. J. Durrett to Mrs. Agnes M. Sullivan, Elizabeth, NJ, Sept. 16, 1940.

By the following winter, pressure on the FDA to approve the drug was mounting as media attention increased. An article in *Reader's Digest* promised that women would find welcome relief from the horrors of menopause if only the FDA would approve DES: "Called by one clinician 'the most valuable addition to our therapy in recent years,' the first synthetic estrogen, diethylstilbestrol ... awaits only the approval of the Federal Food and Drug Administration as a 'new drug' before being placed on the market as an inexpensive, orally-administered therapeutic agent for the relief of the menopause and other conditions. ... Stilbestrol will be welcomed because it will extend the treatment of one of the most distressing of natural body processes: the emotional stress, irritability, mental depression, exhaustion, and physical upsets that accompany 'change of life' in women between the ages of 40 and 50." Media clipping, Helen Haberman, "Help for Women Over Forty," from *Reader's Digest* November 1941. In FDA, NARA. RG 88, Records



- of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1941. Folder 526.1 Nov-Dec. Dr. James Davis from Statesville, North Carolina, wrote to the FDA on Feb. 4, 1941: "Is there a possibility that the manufacturers will be able to put this [drug] on the market any time soon? My experience with this drug has been so satisfactory that I feel it should be available." FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1941. Folder 526.1 January to July. Letter, Dr. James W. Davis (Statesville, NC) to Dr. J. J. Durrett, FDA. 2/7/41.
24. Susan Bell analyzes the contents of these case reports in "Gendered Medical Science."
  25. James C. Whorton, *Before Silent Spring: Pesticides and Public Health in Pre-DDT America*, (Princeton: Princeton University Press, 1974), 225.
  26. FDA, FIO. DES Microfiche # 166. Folder 159. Memorandum to Dr. Herbert C. Calvery RE: Literature on Stilbestrol, Feb. 29, 1940.
  27. Hugh Auchincloss, a scientist at Columbia, was one of the most prominent researchers leading the charge against DES on suspicion of cancer. Joined by a fellow researcher, Cushman Haagensen of Columbia, and by the editor of *The Journal of the American Medical Association*, Auchincloss warned in JAMA of "the danger of cancer from the now widely used female sex hormone treatment." Auchincloss identified one case of breast cancer developing in a woman who had been treated with estrogen (not diethylstilbestrol) for just over two years, while the JAMA editor noted that among forty-three women treated with estrogen in England, three of them had development "cancer of the womb." FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1940. Folder 526.1-13. Press clipping from The Press-Scimitar, Memphis, Tennessee, May 20, 1940. "Cancer danger in hormone use."
- The lawsuit against the American Medical Association made other scientists unwilling to risk testifying against pharmaceutical companies. For example, Dr. Robert T. Frank, a scientist whom the FDA had wanted to testify in a case against a topical estrogen cream, refused because of his bitterness over the way "he had been treated when making his deposition in the A.M.A.-Endocrine case. He referred to the personal abuse heaped upon me both before and since testifying." Memorandum of interview. Dr. Robert T. Frank, New York, and Dr. Gordon A. Granger, Medical Officer of the FDA. July 11, 1940. In FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1940. Folder 526.1-11. For a revealing summary of the endocrine case, see Memorandum 10/1/41. George Larrick, Acting Chief, New Drug Division, to Walter Campbell, Commissioner. In FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1941. Folder 526.1. October.
28. For example, one doctor expressed concern that label warnings "might bring repercussions on the physician should a patient develop carcinoma during estrogenic therapy." Memorandum of interview. Dr. Samuel Sorkin, Chicago, and Dr. Gordon A. Granger, Medical Officer of the FDA. August 1, 1940. in FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1940. Folder 526.1-11.
  29. The FDA required all manufacturers in 1941 to include the warning: "The administration of stilbestrol is contraindicated if the patient is in the age group where continued ovarian function and fertility are desirable, due to the alleged inhibitory activity of stilbestrol on anterior pituitary function." FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1941. Folder 526.1 Nov-Dec. letter, W. G. Campbell, Commissioner of FDA, to Merck & Co., re NDA 4076, 11/3/41.

On October 23, 1941, Dr. Joseph Rosin of Merck asked the FDA to justify the inclusion of this statement. Commissioner Walter Campbell replied: "First and primarily, we feel that promotional material regarding stilbestrol should be extremely conservative in order that practitioner may not be encouraged to use the drug in conditions where deleterious

results may ensure. In our judgment, a few instances of sterility produced by this drug would be cause for serious concern on the part of all interested parties, and particularly so if the descriptive literature did not forthrightly inform the practitioner that such a consequence is a possibility." FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1941. Folder 526.1 Nov-Dec. letter, W. G. Campbell, Commissioner of FDA, to Merck & Co, re NDA 4076, 11/3/41.

Merck wrote back again, insisting that some doctors felt DES wouldn't impair fertility, and Commissioner Campbell replied: "A goodly number of qualified experts have recommended that the administration of the drug be restricted in the manner suggested by the sentence under discussion. A discussion as to the merits of the different viewpoints held by experts in this field would not appear to be particularly fruitful at this time. ... In conclusion it might be well to again state that the main reason for the suggested revision of this sentence is conservatism, and in our judgment the public interest may well be served by the exercise of conservatism with respect to this drug at this time." FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1941. Folder 526.1 Nov-Dec. letter, W. G. Campbell, Commissioner of FDA, to Merck & Co, re NDA 4076.

30. In a memo to all stations, the FDA office wrote: "We quote for your information and guidance the Administration's June 1, 1942 letter to West District ... While the possibility of developing a prosecution based on the over-the-counter sale of a dangerous drug received in interstate commerce is still being considered, only the most carefully chosen case will be discussed with the General Counsel's office initially ... As of course you know, some question has been raised as to the applicability of the terms of the Federal law to over-the-counter sales of products. ... When the courts are called upon to give judgment in a matter of this kind, we would like to have the decision based on a case which involves a more serious public health hazard than is exhibited by stilbestrol. ... For this purpose one of the sulfanilamide drugs in table form would be particularly appropriate, since the element of danger could be convincingly demonstrated." FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1942a. Folder 526.1-.10-526.3-.66 Memo, W. R. M. Wharton, Chief, Eastern District, to Stations, Eastern District: 6/25/42.
31. In October of 1945, Abbott asked the FDA to allow them to drop warnings: "In view of the satisfactory clinical experience with Diethylstilbestrol during recent years, we suggest the Food and Drug Administration permit the omission from our labels of the statement, "Warning—This is a potent drug and serious consequences may result if used other than under constant medical supervision." The FDA wrote back: "As you point out, experience during the last four years has demonstrated that with therapeutic dosages of this drug the toxic reactions have not been greater, either in number or severity, than those seen with therapeutically equivalent amounts of the natural estrogens. For this reason, we are inclined to agree with you that the warning quoted above is no longer necessary on preparations of diethylstilbestrol in the usual dosage forms." FDA, FIO. DES Microfiche # 20, folder 11, Letter, Edgar B. Carter, Associate Director of Research, Abbott Laboratories, to Dr. Walton Van Winkle, Jr. FDA, 10/3/45. And FDA, FIO. DES Microfiche # 20, Folder 11. Letter, P. B. Dunbar, Commissioner of Food and Drugs, FDA, to Mr. Edgar B. Carter, Abbott Laboratories, 10/26/45.
32. In 1946, Karnaky wrote to Squibb requesting more experimental drug samples, "I would like to have you continue sending me the 25 mg stilbestrol each month for at least 12 more months. ... I would like to continue playing with stilbestrol and see what other uses we can work out for it. Personally, I believe it is a wonderful drug." FDA, Freedom of Information Office, 5600 Fisher Lane, Rockville, Maryland (hereafter FIO). DES Microfiche # 35, Folder 18/4/19, Letter from Dr. Karnaky to Dr. Newcomer of E.R. Squibb and Sons, 1946. In another instance, he "offered to finance the funeral costs 'up to

- \$1000' of anyone who died from an excessive dose" of DES. Karnaky to King, June 3, 1947, Karnaky File, FDA records; cited in Gillam and Bernstein, "Doing Harm," 67. The Karnaky quote about the drug companies is also from Gillam and Bernstein, "Doing Harm," 67.
33. FDA, FIO. DES Microfiche # 26, Folder 17, NDA 4056. Material from H. Sidney Newcomer, Medical Department, E.R. Squibb and Sons, to R. P. Herwick, FDA. 4/28/47.
  34. White's work, limited to diabetic women, lacked controls and did not indicate how many women had even been given various hormones, or in what combinations. P. White, "Pregnancy Complicating Diabetes," *The Journal of the American Medical Association* 128 (May 19, 1945): 181-82; and White and Hazel Hunt, "Pregnancy Complicating Diabetes," *Journal of Clinical Endocrinology* 3 (September 1943): 500-11. For criticisms of this work, see David Hurwitz and Katherine Kuder, "Fetal and Neo-natal Mortality in Pregnancy Complicated by Diabetes Mellitus," *The Journal of the American Medical Association* 124 (January 29, 1944): 271-75; and the comments of William Dieckmann in White, "Pregnancy Complicating Diabetes," 182. The Smiths' 1946 study provided data on neither efficacy or safety; they described the outcome from only one woman's pregnancy: Olive W. Smith, George V. S. Smith, and D. Hurwitz. 1946. Increased excretion of pregnanediol in pregnancy from diethylstilbestrol with special reference to the prevention of late pregnancy accidents," *American Journal of Obstetrics and Gynecology* 51 (1943): 411-415. Described in Gillam and Bernstein, "Doing Harm," 68. See also Olive Smith, "Diethylstilbestrol in the Prevention and Treatment of Complications of Pregnancy," *American Journal of Obstetrics and Gynecology* 56 (1948): 821-34.
  35. FDA, FIO. DES Microfiche # 26, Folder 17, NDA 4056. Material from H. Sidney Newcomer, Medical Department, E.R. Squibb and Sons, to R. P. Herwick, FDA. 4/28/47. This file includes testimonies from doctors who gave DES to their patients and reported on the outcomes to Dr. Newcomer. The doctors' names and the patients' names have been removed from the files. The specific testimony regarding "excessive shopping" is from a letter to Dr. Newcomer dated November 19, 1946.
  36. These studies were included in the annotated bibliography prepared by Merck and Co., April 1941, submitted to the FDA. *Stilbestrol (Diethylstilbestrol): Annotated Bibliography*.
  37. Noble, "Functional Impairment of the Anterior Pituitary Gland," 177-83. Just months after the synthesis of DES, Noble's work showed that the injection into rats of DES in oil solutions was followed by atrophy of the testes, prostate, and seminal vesicles in the male, ovarian atrophy in the female, and an increase in the weight of the adrenals and pituitary in both sexes. Low doses of DES were often more toxic than high doses, so DES didn't follow the normal dose-response relationships expected by toxicology. This observation led some scientists within the FDA to urge particular caution, while leading other scientists and regulators within the FDA to dismiss its potential for harm.
  38. For example, R. R. Greene et al. (1939) showed that DES modified embryonic sexual development in the male rat: "Eighteen male and 28 female offspring were delivered by 12 or 30 rats which had been treated with diethylstilbestrol from the 12th or 13th day of pregnancy until a day or two before the expected date of delivery. ... In both males and females the external genitalia of the newborn were of the female type and nipples were present," in *Stilbestrol (Diethylstilbestrol): Annotated Bibliography*, 7. A French researcher, E. Wolff, showed that DES altered sexual development in chicken embryos (1939), while J. H. Gaarenstroom (1939) showed that when chicken eggs were injected with DES on the second day of brooding, all the hatchlings were female—no cocks were hatched. Albert Raynaud (1939) also showed feminization of male embryos when their mothers were treated with DES, while R. R. Greene et al. (1940) showed that DES injections in pregnant rats (10.0 to 42.0 mgm), the male babies showed inhibition of normal male development—prostates were absent and seminal vesicles were absent. When the male rats were born, their testes appeared normal, but when they reached

puberty, their testes developed cryptorchidism. When female rats were born, their genitalia also appeared normal, but when they reached puberty, their vagina and urethra proved to share a common orifice, and the ovaries were excessively small. All in *Stilbestrol (Diethylstilbestrol): Annotated Bibliography*. A. S. Parkes et al. showed that DES could prevent implantation in rabbits, and that it was "highly effective in interrupting established pregnancy in rabbits." A. S. Parkes, E. C. Dodds, and R. L. Noble, in "Interruption of Early Pregnancy by Means of Orally Active Estrogens," *British Medical Journal* 2 (1938): 557-59.

39. R. R. Greene, "Embryology of Sexual Structure and Hermaphroditism," *Journal of Clinical Endocrinology* 4 (July 1944): 335-48. In 1959, a clinician described a case of male intersex in an infant exposed to DES, and cited Greene's essay as having anticipated this effect in humans: N. M. Kaplan, "Male Pseudohermaphroditism: Report of a Case, with Observations on Pathogenesis," *NEJM* 261 (September 24, 1959): 642-43. Cited in Gillam and Bernstein, "Doing Harm," 70.
40. Rosenblum and Melinkoff, "Preservation of the Threatened Pregnancy," *Western Journal of Surgery* (1947): 601-03. Another researcher noted "the possibility of some latent effects on the reproductive and endocrine system of the infant," Bernard Lapa, "Diethylstilbestrol in the Treatment of Idiopathic Repeated Abortion," *New York State Journal of Medicine* 48 (December 1, 1948): 2614. Both cited in Gillam and Bernstein, "Doing Harm," 67, 68.
41. Other researchers criticized the research of George and Olive Smith because of its absence of control groups, placebos, and blinding to correct for chance results or bias. David Hurwitz in 1941—who had collaborated with the Smiths—insisted that "studies could not confirm the efficacy of prenatal DES in humans unless patients were assigned, alternately, to a treatment and to a control group, so that results could be compared." David Hurwitz, "Pregnancy Accidents in Diabetes," *The Journal of the American Medical Association* 116 (February 15, 1941): 645.

In 1953, the first double-blind, controlled study of prenatal DES, led by William Dieckmann and published in *The American Journal of Obstetrics and Gynecology*, indicated that DES "was not effective in preventing miscarriages ... in either seemingly normal or troubled pregnancies. Not only did DES not work, some slivers of evidence actually suggested that it was worse than a placebo." W. J. Dieckmann et al., "Does the Administration of Diethylstilbestrol during Pregnancy Have Therapeutic Value?" *The American Journal of Obstetrics and Gynecology* 66 (November 1953): 1062-75.

42. D. Lindsey Berkson, *Hormone Deception: How Everyday Foods and Products Are Disrupting Your Hormones—and How to Protect Yourself and Your Family* (Chicago: Contemporary Books 2000), 62-63.
43. For a discussion of the regulatory process in livestock, see Marcus, *Cancer From Beef*, 11-25.
44. For examples, see letter, Mrs. Edgar G. Eder, Chicago, to FDA (answered by Klumpp), December 2, 1940. Response, Klumpp to Eder, January 14, 1941. Response, Eder to Klumpp, January 16, 1941. In FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1941. Folder 526.1 January to July. 49. FDA, NARA.
45. The owner of Arapahoe chemicals of Colorado wrote to the FDA: "Our Company has recently been approached in regard to manufacturing stilboestrol ... as raw materials for pharmaceutical formulation. We know that these materials are all readily absorbed through the skin and by inhalation. It is our belief that the physiological effect of these materials would constitute a decided industrial hazard. In order to properly evaluate the advantages of undertaking the manufacture of synthetic estrogens, it is necessary that we obtain as much information as possible about them in regard to the seriousness of the health hazard involved, recommended precautions for handling, treatment of affected individuals, cumulative effects, etc. We are particularly concerned over the

possibility of carcinogenesis through long continued contact with stilboestrol." FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1947. Folder 526.1. Letter, Richard Waugh, Technical Director, Arapahoe Chemicals, Inc. to Dr. Robert Stormont, FDA. 6/26/47. The FDA responded: "we have your letter of June 26, 1947 requesting information concerning the health hazard involved and the precautions necessary on the manufacture of stilbestrol ... It is our understanding that excessive exposure to the substances may cause marked disturbances of the menstrual function in women and have a devirilizing effect in men. For this reason it might be feasible for you to consider the employment of old rather than young men if adequate precautionary measures cannot be instituted. The question of carcinogenic potentiality of these substances is one which cannot be answered with finality at this time. We regret to be unable to be of much assistance to you in this matter and suggest that you write to the Bureau of Industrial Hygiene of the United States Public Health Service the National Institute of Health, Bethesda, Maryland for further information." FDA, NARA. RG 88, Records of the Food and Drug Administration, A1, Entry 5, General Subject Files, 1938-1974. 1947. Folder 526.1. Handwritten comments by FDA staff on the Letter, Dr. Robert Stormont, FDA, to Richard Waugh, Technical Director, Arapahoe Chemicals, Inc. 7/9/47.

46. Since 1975, the FDA has required drug labeling to include a subsection on a drug's ability to cause birth defects and other effects on reproduction and pregnancy.
47. Editorial staff, "An Environment for Development," *Environmental Health Perspectives* 107 (1999). For recent research on second and third generation DES effects, see, R. H. Kaufman et al., "Continued Follow-Up of Pregnancy Outcomes in Diethylstilbestrol-Exposed Offspring," *Obstetrics and Gynecology* 96 (2000):483-89; Retha Newbold, "Cellular and Molecular Effects of Developmental Exposure to Diethylstilbestrol: Implications for Other Environmental Estrogens," *Environmental Health Perspectives* 103, Supplement 7 (1995); Retha R. Newbold et al., "Proliferative Lesions and Reproductive Tract Tumors in Male Descendants of Mice Exposed Developmentally to Diethylstilbestrol," *Carcinogenesis* 21 (2000):1355-63.; Retha R. Newbold et al., "Increased Tumors but Uncompromised Fertility in the Female Descendants of Mice Exposed Developmentally to Diethylstilbestrol," *Carcinogenesis* 19 (1998): 1655-63.
48. Apfel and Fisher, *To Do No Harm*.
49. Gillam and Bernstein in "Doing Harm" write "In fact, agency regulators, never doubting the drug's efficacy, clearly wanted to approve DES if the explosive safety issue could somehow be defused. By late 1940, perhaps responding to industry suggestions, FDA officials had hatched a plan to do precisely this.... Had the FDA wanted to avoid approving DES, it possessed the statutory authority to do so. Had the agency wished to resist the pressures for approval, it could always have delayed (it had done so before), rejected the Master File tactic ... stressed the unsettling animal data, and given dissident experts a serious hearing," 65-66. While the FDA did accept the Master File, many FDA drug staff and scientists actively resisted the Small Committee's efforts, and never gave up their increasingly bitter fight to block DES approval.
50. Philip Hiltz, *Protecting America's Health*, 119. Hiltz describes one agent's remark that inspectors who led the FDA during the 1950s were "the rat-turd counters," 118. The appointment of George Larrick as FDA commissioner in 1954 illustrates how co-opted the FDA was becoming by the industry it was supposed to be regulating. Industry lobbying got Larrick nominated, for Larrick "believed in the mission of the drug industry, and had preached cooperation and harmony between the regulators and the companies as he rose through the ranks," 119.
51. Sze, "Boundaries and Border Wars," 795.
52. Gillam and Bernstein, "Doing Harm," 68.
53. Barbara Seaman, *The Greatest Experiment Ever Performed on Women: Exploding the*



- Estrogen Myth* (New York: Hyperion, 2003). "Medical policy on estrogens has been to 'shoot first and apologize later'—to prescribe the drugs for a certain health problem and then see if there is a positive result. Over the years, hundreds of millions, possibly billions of women, have been lab animals in this unofficial trial. They were not volunteers. They were given no consent forms. And they were put at serious, often devastating risk," 5. A nuanced view of the ways ideas about gender influenced DES research is in Susan Bell, "Gendered Medical Science."
54. FDA, FIO. DES Microfiche # 0004. Folder 3. Dec. 26 1941, Proposed Lilly Circular on stilbestrol, NDA 4041.
  55. Ann Dally, "Thalidomide: Was the Tragedy Preventable?" *Lancet* 351 (1998): 1197-99. For a fascinating exploration of contrasts between drug regulation in Germany and the United States, and the ways those contrasts influenced responses to thalidomide, see Arthur Daemmlich, "A Tale of Two Experts: Thalidomide and Political Engagement in the United States and West Germany," *Social History of Medicine* 15 (2002): 137-58.
  56. Cadbury, *Altering Eden*, 48. One possible objection to the argument that few researchers imagined DES could cross the placenta comes from the fact that in 1941, the FDA forbade the use of DES in pregnant women, implying that regulators were concerned about potential effects on the fetus. The DES warning labels, however, show that regulators were not concerned about DES crossing the placenta and causing birth defects; rather, they were concerned that DES could harm the uterus and ovarian function, which would indirectly be a concern for pregnancy.
  57. Some doctors and researchers were concerned, just not in the FDA or the industry. In 1949, an editor of *The Journal of the American Medical Association* warned "one must not lose sight of the fact that there is a possibility that large doses of female sex hormones may affect a male fetus adversely." Reports began coming out in the medical literature about intersex conditions in children exposed to DES in utero. See, for example, A. M Bongiovanni, A. M. DiGeorge, M. M. Grumbach, "Masculinization of the Female Infant Associated with Estrogenic Therapy Alone During Gestation: Four Cases," *Journal of Clinical Endocrinology* 19 (August 1959): 1004-11; N. M. Kaplan et al., "Apparent Masculinization Of Female Fetus Diagnosed as True Hermaphroditism by Chromosomal Studies," *Journal Of Pediatrics* 60 (1962): 540.
  58. Scott Gilbert, "The Genome in its Ecological Context: Philosophical Perspectives on Interspecies Epigenesis," *Annals of the New York Academy of Sciences* 981 (2002): 202-18.
  59. Linda Nash, *Inescapable Ecologies: A History of Environment, Disease, and Knowledge* (Berkeley and Los Angeles: University of California Press, 2006).
  60. USDA, "A Primer on Beef Hormones," February 24, 1999; <http://stockholm.usembassy.gov/Agriculture/hormone.html>
  61. S. Nandi et al., "Estrogen Can Prevent Breast Cancer by Mimicking the Protective Effect of Pregnancy," In *Hormonal Carcinogenesis*, vol. 4, ed. J. J. Li et al. (London: Springer-Verlag, 2005), 153-65; and L. Rajkumar et al., "Short-Term Exposure to Pregnancy Levels of Estrogen Prevents Mammary Carcinogenesis," *Proceedings of the National Academy Science* 98 (2001): 11755-59.
  62. René Dubos, cited in Joe Thornton, *Pandora's Poison: Chlorine, Health, and a New Environmental Strategy* (Cambridge: MIT Press, 2000). For a longer discussion, see René Dubos, *Mirage of Health: Utopias, Progress, and Biological Change* (New York: Harper & Brothers, 1959).